**Activation of Innate Immunity Leads to Accelerated Development of Sjogren's Syndrome-Like Disorder in NZB/W F1 Mice**

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**Purpose:**
To determine whether chronic activation of innate immunity in genetically susceptible individual will lead to accelerated adaptive immune response and development of Sjögren's syndrome (SS).

**Methods:**
Female NZB/W F1 mice were treated every other day for 2 weeks, either with TLR3 agonist poly (I:C) or PBS. Mice were monitored for the development of SS-like disorder by checking pilocarpine induced saliva flow. Submandibular glands (SMG) were analyzed for lymphocytic infiltration and cell types within the infiltrates were characterized by immunohistochemistry. Gene expression levels of inflammatory cytokines within the SMG were determined by real time PCR. Sera were analyzed for presence of autoantibodies to Ro60 and La. Antibody deposition within the SMG was studied by immunofluorescence.

**Results:**
Repeated injections of poly I:C rapidly induced salivary gland dysfunction that was independent of systemic or localized adaptive immune response. The glandular function recovered completely within 2-3 weeks after the cessation of poly I:C treatment. However, by 4 months post-treatment, the mean saliva volume in poly I:C treated group was significantly lower than the PBS treated group and was associated with severe lymphocytic infiltration within the SMG. The lymphocytic infiltrates were mainly composed of CD4+ T and B cells. In comparison with PBS treated mice, the SMGs from poly I:C treated mice showed significantly higher levels of Il-12a, IL-21 and IL21R gene expression. While IL-17F expression was detected in both groups, IL-17A expression was undetectable. Characterization of CD4+ T cells within the infiltrates showed presence of ICOS+, CXCR5+ cells. The levels of anti-Ro60 and anti-La antibodies were significantly higher in the poly I:C treated group and the SMG from these mice showed IgM and IgG deposition.

**Conclusion:**
Our data suggests a biphasic model for SS development. In the initial phase, chronic activation of innate immunity causes glandular dysfunction. This predisposes the salivary gland for an assault by accelerated adaptive immune response in the later phase. An ensuing localized T-B cell response causes glandular destruction and loss of function. Our data also demonstrates for the first time that IL-21 producing follicular T helper cells (Tfh) and their interaction with B cells within the SMG could be critical for the pathogenesis of SS. Thus, the Il-21 pathway might provide a promising target for future immunotherapy of SS.